JACC Vol 2, No. 4
October 1983:652–60

The Acute Effects of Low Flow Oxygen and Isosorbide Dinitrate on Left and Right Ventricular Ejection Fractions in Chronic Obstructive Pulmonary Disease

DOUGLASS MORRISON, MD, FACC, JAMES CALDWELL, MD, S. LAKSHMINARYAN, MD, JAMES L. RITCHIE, MD, FACC, J. WARD KENNEDY, MD, FACC

Tucson, Arizona and Seattle, Washington

The objectives of this study were to determine the effects of low flow oxygen and isosorbide dinitrate on rest and exercise biventricular ejection fractions in patients with chronic obstructive pulmonary disease and to relate these ejection fraction responses to changes in pressure and flow. Nine patients with stable, moderate to severe chronic obstructive pulmonary disease who had no prior history of heart failure performed supine exercise with simultaneous hemodynamic and radionuclide ventriculographic monitoring. Eight patients performed a second exercise during low flow oxygen breathing and five performed a third exercise after ingesting 10 mg oral isosorbide. Oxygen led to a decrease in exercise pulmonary artery pressure in all subjects and a decline in total pulmonary resistance in five of the seven in whom it was measured. Right ventricular ejection fraction increased 0.05 or more only in subjects who had a decrease in total pulmonary resistance. Isosorbide led to an increase in rest and exercise right and left ventricular ejection fractions with simultaneous decreases in pulmonary artery pressure, total pulmonary resistance, blood pressure and arterial oxygen tension.

These results suggest that in patients with chronic obstructive pulmonary disease but without a history of right heart failure, the right ventricular systolic functional response to low flow oxygen and isosorbide at rest and exercise is, in part, determined by changes in total pulmonary resistance. The chronic relation between right ventricular ejection fraction and pulmonary hemodynamics in patients with chronic obstructive pulmonary disease remains to be evaluated.

Hypoxic vasoconstriction can produce elevation of pulmonary artery pressure, which in turn can lead to right ventricular hypertrophy, dilation and failure (1–3). Low flow oxygen therapy is effective in lowering pulmonary artery pressure in many patients with chronic obstructive pulmonary disease, but it is expensive, inconvenient, potentially toxic and ineffective in some patients (4–11). The hemodynamic responses to low flow oxygen cannot be accurately predicted from measurements of arterial oxygen tension (P_{O_2}) (8). Therefore, direct hemodynamic measures are required to assess the response of the pulmonary vasculature to oxygen therapy. Similarly, it has been shown that a number of vasodilators are also effective in lowering pulmonary artery pressure in patients with chronic obstructive pulmonary disease (12–15). Among these vasodilators, oral nitrates are used frequently for concomitant ischemic cardiovascular disease (12–14).

We recently developed and validated a method of gated blood pool radionuclide ventriculographic measurement of right ventricular ejection fraction (16,17). The blood pool study can also be analyzed for left ventricular ejection fraction. In rest studies, it has been shown that the right ventricular ejection fraction is related inversely to pulmonary artery pressure (18–20). This relation is complicated by a number of other factors, such as the presence of right ventricular infarction, tricuspid regurgitation or severe left ventricular dysfunction (20). In normal subjects, exercise right ventricular ejection fraction appears to be inversely related to total pulmonary resistance (17).

The current study sought to: 1) test the effect of low flow oxygen and isosorbide on rest and exercise right and left

From the Cardiology and Nuclear Medicine Sections, Tucson VA Medical Center and University of Arizona, Tucson, Arizona and the Cardiology, Nuclear Medicine and Pulmonary Sections, University of Washington and Seattle VA Medical Center, Seattle, Washington. This work was supported by the Medical Research Service, Tucson and Seattle VA Medical Centers, and the Department of Internal Medicine, University of Arizona. Manuscript received September 7, 1982; revised manuscript received April 7, 1983, accepted May 11, 1983.

Address for reprints: Douglass Morrison, MD, Cardiology Section (111C), Tucson VA Medical Center, Tucson, Arizona 85723

0735-1097/83/$3 00

ventricular ejection fractions in patients with chronic obstructive pulmonary disease, and 2) compare the ejection fractions with simultaneous measures of pressure and flow.

Methods

Study patients. Nine patients with stable, moderate to severe chronic obstructive pulmonary disease and no history of heart failure were studied. Ages, pulmonary function data, medications and electrocardiographic data from the nine patients are listed in Table 1. All patients had a forced expiratory volume in 1 second of less than 65% of the predicted value, a forced expiratory volume/forced vital capacity ratio of less than 70% and a total lung capacity greater than 75% of predicted (21,22). All patients were smokers and all had a chronic cough.

No patient had evidence of primary left heart abnormality by history, physical examination, 12 lead electrocardiogram or chest X-ray film. No patient had a prior history of heart failure. Because of the difficulty in separating right heart failure in cor pulmonale from right heart failure secondary to left heart failure on clinical grounds (23,24), this exclusion eliminated all patients with cor pulmonale. Because patients served as their own controls, they were maintained on their stable medications. Informed consent was obtained from all patients using forms approved by the University of Washington Human Subjects Committee.

Hemodynamic measurements. Before the actual testing, all subjects performed an exercise test to familiarize themselves with the equipment. On the day of the test, subjects refrained from drinking coffee or tea or smoking cigarettes. A triple lumen thermodilution Swan-Ganz catheter was introduced from the basilic vein to the right pulmonary artery. A plastic catheter was placed percutaneously in the radial artery. The patient was then transported to the nuclear imaging suite for exercise testing. Patients performed graded exercise using a supine bicycle ergometer (Quinton Instruments).

All subjects had a rest baseline and graded exercise study during room air breathing. After 30 minutes' rest, repeat baseline studies were obtained and all subjects were given oxygen at 4 liters/min via nasal prongs for 30 minutes. A post-oxygen rest study was obtained and subjects performed a second graded exercise while breathing oxygen; one subject could not perform a second exercise. Oxygen administration was discontinued and the subjects then rested for 30 minutes; five agreed to ingest a 10 mg isosorbide dinitrate tablet and perform a third exercise. Thirty minutes after ingestion, a repeat rest study and a third graded exercise were performed. For each exercise, subjects began pedaling at 200 kilopond-meters (kpm)/min and increased 200 kpm/min for each 4 minute stage until symptom-limited maximum was reached. This is the same exercise protocol by which normal volunteers have been studied (17).

Twelve lead electrocardiograms were obtained during each baseline period and during each stage of exercise. Arterial blood pressure, pulmonary artery pressure, pulmonary wedge pressure and central venous pressure measurements were made at each baseline and during the last 2 minutes of each stage of exercise using Ailtech MS-20AA 15FA strain gauges and an Electronics for Medicine VR 8 recorder. Zero reference was midthorax and electrical mean

Table 1. Clinical and Pulmonary Function Data in Nine Patients

Case	Age (yr)	Medications	FEV_1 (liters, % predicted)	FEV_1/FVC (%)	Rest Arterial Blood Gases (mm Hg)			ECG
					P_{O_2}	P_{CO_2}	pH	
1*	56	None	1 92;62	57	75	33	7 44	Early repol
2	56	Isoproterenol; medihaler	1 38,46	50	59	40	7 39	PRWP
3	61	Aminophylline	1 26,47	41	68	40	7.44	NSST
4	60	Aminophylline	1 39;46	51	54	43	7.42	P pulmonale, PRWP
5	59	Aminophylline	2 02;65	62	68	37	7 39	Normal
6	63	Isoproterenol; medihaler	1 89;64	61	87	34	7 42	Normal
7	61	Aminophylline, isoproterenol, medihaler	0 77;29	42	74	46	7 39	P pulmonale, PRWP
8	63	Aminophylline	0 74;33	39	66	41	7 49	P pulmonale, RBBB
9	61	Isoproterenol; medihaler	1.51;50	38	72	40	7 42	PRWP

*This patient had a normal coronary arteriogram, contrast ventriculogram and exercise/redistribution thallium study 1 year before this study.

ECG = electrocardiogram; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity, NSST = nonspecific ST-T wave abnormalities; P_{CO_2} = partial pressure of carbon dioxide; P_{O_2} = partial pressure of oxygen, PRPW = poor R wave progression; RBBB = right bundle branch block; repol = repolarization.

JACC Vol. 2, No 4
October 1983:652–60

pressures averaged over at least three respiratory cycles were recorded.

Radial artery samples were obtained at each baseline and during the last 2 minutes of each exercise stage for blood gas measurements which were performed with standard electrodes.

Thermodilution cardiac output measurements were performed in triplicate during each baseline period and once during each exercise period. For the baseline period, the mean of the three measures is reported.

Total pulmonary resistance was calculated by the formula: total pulmonary resistance [dynes·s·cm^{-5}] = (mean pulmonary artery pressure [mm Hg] × 80)/CO_{TD}; where CO_{TD} is the thermodilution cardiac output in liters/min. Systemic resistance was calculated by the formula: Systemic resistance [dynes·s·cm^{-5}] = (mean blood pressure [mm Hg] × 80)/CO_{TD} liters/min.

Radionuclide imaging measurements. Ten milliliters of venous blood was withdrawn and the red blood cells labeled in vitro with 30 mCi of technetium-99m (25). The labeled red blood cells were then reinjected and allowed to equilibrate before imaging. Imaging was performed using a low energy, high sensitivity, parallel-hole collimator and an Ohio Nuclear series 100 gamma scintillation camera interfaced with a dedicated computer system (Modumed Medical Data Systems, Medtronic). Count and image acquisition occurred under electrocardiographic control such that corresponding 40 ms segments of each cardiac cycle were screened and stored in the computer core memory; all patients were in sinus rhythm. Images were obtained as 64 × 64 matrixes. Commercially available software (MDS:MUGX) was used for acquisition. Studies were acquired in the left anterior oblique view which provided best ventricular separation.

During the first baseline rest study, a count targeted (300 K) and 2 × 2 minute acquisitions were obtained. Thereafter, a 2 minute acquisition during the last 2 minutes of exercise and for each baseline period was acquired. The first baseline ejection fractions reported are the mean of the 300 K and 2 × 2 minute acquisitions.

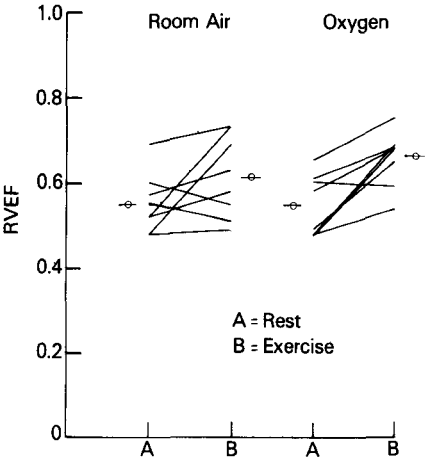
The images were converted from the MDS-Modumed computer system in which they were acquired onto MDS-A^2 software for analysis in Tucson. Before quantitative analysis, all images were viewed in cine mode. The same computer-selected variable region of interest method, using commercially available software (MDS-A^2:ejection fraction), was applied to both left and right ventricular quantitative analysis. This method has been described in detail for the right ventricle in the validation study from this laboratory (16).

*Briefly, a box was placed around the ventricle on the first frame or image.*The operator set thresholds for each of four quadrants around the box so that a continuous line was drawn around the ventricle on this image. The thresholds were determined by the zero point of the two-dimensional second derivative with respect to time. The computer used this box and thresholds to draw a separate ventricular region for each frame. The operator viewed these regions and determined whether to accept or alter them. It was seldom necessary to alter any of the left ventricular regions, but it was frequently necessary to alter right ventricular systolic frames as in the right ventricular validation study (16). The most frequent alteration was removal of atrial pixels in the upper left quadrant. The computer-selected left ventricular background, expressed as counts per pixel, was subtracted from each frame. With use of the respective regions of interest, background-corrected time-activity curves were obtained for both the right and left ventricles.

The ejection fractions were calculated from the formula: ejection fraction = stroke counts/end-diastolic counts, where end-diastolic counts = the peak of the time activity curve, usually the first frame, end-systolic counts = the trough and stroke counts = end-diastolic counts − end-systolic counts. When blood pool studies are processed in this manner, the right ventricular ejection fraction is highly reproducible and there is a strong correlation between blood pool and gated first pass right ventricular ejection fraction ($n = 22$; correlation coefficient [r] $= 0.93$; $Y = 0.03 + 0.89X$; standard error of the estimate $= 0.04$) and the left and right ventricular stroke counts are in close agreement ($n = 19$; $r = 0.86$; $Y = 73 + 0.089X$; SEE = 116 counts on 300 K images) (16). The left ventricular ejection fraction obtained by this method correlates well with both contrast angiography ($n = 32$; $r = 0.82$; $Y = 0.15 + 0.66X$ and gated first pass studies ($n = 41$; $r = 0.96$; $Y = 0.00 + 1.01X$) (unpublished data).

Statistical analysis. From the ejection fraction and hemodynamic data, mean and standard deviation were calculated for rest and each exercise stage. Paired *t* tests were

Figure 1. Right ventricular ejection fraction (RVEF) at rest **(A)** and during exercise **(B)** before and after low flow oxygen (4 liters/min).



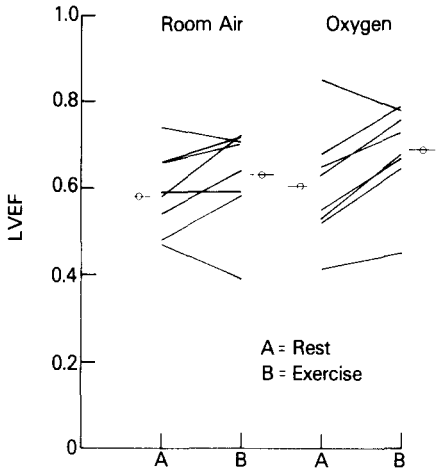


Figure 2. Left ventricular ejection fraction (LVEF) at rest **(A)** and during exercise **(B)** before and after low flow oxygen (4 liters/min).

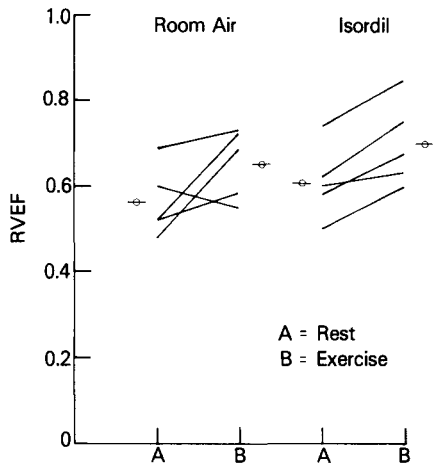


Figure 3. Right ventricular ejection fraction (RVEF) at rest **(A)** and exercise **(B)** before and after 10 mg oral isosorbide dinitrate (Isordil).

used to determine if changes with interventions were significant, with a probability (p) value less than 0.05 considered significant.

Results*

Methodology. There was an excellent correlation between radionuclide left and right ventricular stroke counts (LVSC, RVSC) during room air breathing ($n = 55$ rest and exercise blood pool studies from the nine subjects; $r = 0.98$; $RVSC = -246 + 1.01\ LVSC$); during oxygen breathing ($n = 60$ rest and exercise blood pool studies from eight subjects; $r = 0.93$; $RVSC = -143 + 1.00\ LVSC$); and after isosorbide ingestion ($n = 38$ rest and exercise blood pool studies from five subjects; $r = 0.95$; $RVSC = +71 + 0.96\ LVSC$).

Right and left ventricular ejection fractions. *Room air versus oxygen breathing.* Figure 1 shows rest and maximal exercise right ventricular ejection fractions during room air and oxygen breathing for all eight subjects who performed both exercises. The rest and exercise ejection fractions were not significantly different with oxygen, although there was a trend toward a greater increase in exercise ejection fraction during oxygen breathing.

Figure 2 shows rest and exercise left ventricular ejection fractions during room air and oxygen breathing. The ejection fractions were not significantly different with oxygen, although there was a trend toward increased ejection fraction during oxygen breathing.

Isosorbide dinitrate ingestion. Figure 3 shows the rest and exercise right ventricular ejection fractions during baseline and after isosorbide ingestion for the five subjects who performed both exercises. The rest values were significantly higher after isosorbide ($p < 0.01$), but the maximal exercise values were not. No patient's right ventricular ejection fraction fell with exercise after isosorbide, in contrast to the baseline exercise value.

Figure 4 shows the rest and exercise left ventricular ejection fractions before and after isosorbide ingestion. The rest values were significantly higher after isosorbide ($p < 0.01$) but the exercise values were not. However, all patients demonstrated an increase in left ventricular ejection fraction with exercise after isosorbide.

Hemodynamic data and ejection fractions. Figures 5 and 6 show the mean ± standard deviation of the radionuclide and hemodynamic variables during rest and at each exercise level during room air breathing, oxygen breathing and after isosorbide ingestion.

The right ventricular ejection fraction did not increase significantly with exercise during any of the test conditions. At each stage, it was slightly higher during oxygen breathing and after isosorbide, but the only difference that reached statistical significance was stage I isosorbide versus baseline ($p < 0.05$).

The total pulmonary resistance did not decrease normally with exercise under any of the conditions of testing (17). It was lower during the oxygen and isosorbide exercises, but the only differences that achieved statistical significance were stage I oxygen ($p < 0.05$) and stage II isosorbide ($p < 0.05$ values.

The pulmonary artery pressure increased abnormally during baseline exercise (17). Exercise pulmonary artery pressure was lower with oxygen and after isosorbide, with stage I oxygen ($p < 0.05$) and both rest and all exercise stages after isosorbide (rest $p < 0.01$, stage I $p < 0.01$, stage II $p < 0.001$) reaching statistical significance.

*Tables listing ejection fraction and hemodynamic values for each patient are available from the authors on request

JACC Vol 2, No. 4
October 1983:652–60

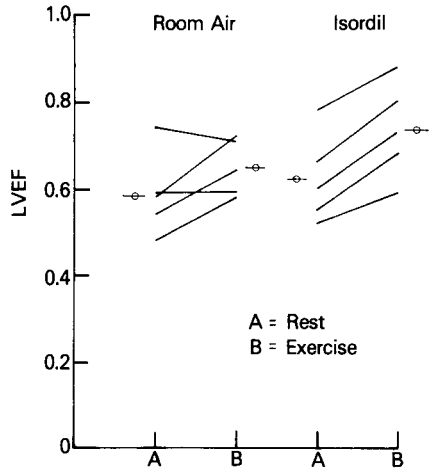


Figure 4. Left ventricular ejection fraction (LVEF) at rest **(A)** and during exercise **(B)** before and after 10 mg oral isosorbide dinitrate (Isordil).

The arterial oxygen tension (PaO_2) fell during baseline exercise. With oxygen breathing, the PaO_2 was higher at rest ($p < 0.05$) and during each exercise stage. The PaO_2 was not significantly different after isosorbide ingestion.

The left ventricular ejection fraction did not increase significantly with baseline exercise. Oxygen did not change rest or exercise left ventricular ejection fraction values. Isosorbide led to significant increases in rest ($p < 0.01$) and stage I exercise ($p < 0.05$) left ventricular ejection fraction values.

The blood pressure increased with exercise under all conditions. Oxygen breathing did not lead to a significant difference in rest or exercise blood pressure. Isosorbide led to lower blood pressure at rest ($p < 0.05$) and during both exercise stages (stage I $p < 0.01$, stage II $p < 0.001$).

Although the exercise was performed supine, significant increases in stroke volume occurred under all conditions. There was no significant difference in stroke volume at rest or during exercise with oxygen. There was a fall in rest stroke volume after isosorbide ($p < 0.05$) but exercise stroke volume was not significantly different from the baseline value.

The heart rate increased with exercise under all conditions. Rest heart rate was higher ($p < 0.05$) after isosorbide. Rest and exercise heart rate during oxygen breathing and exercise heart rate after isosorbide ingestion were not different from the baseline value.

Discussion

Relation between pulmonary artery pressure and resistance and right ventricular ejection fraction. Recent studies (18) of patients with chronic obstructive pulmonary

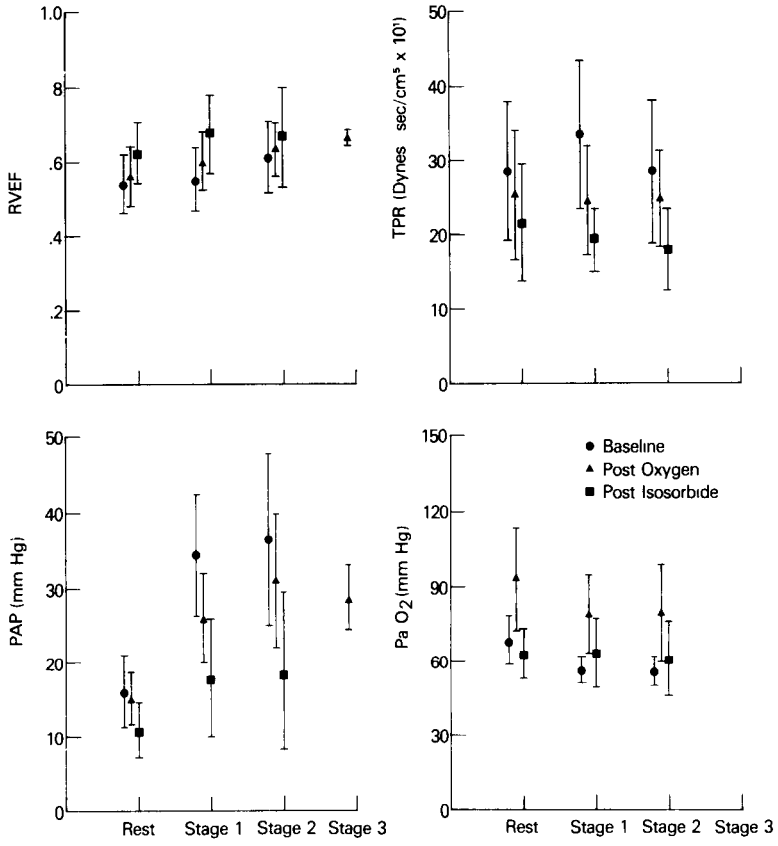


Figure 5. Rest and exercise right ventricular ejection fraction (RVEF), total pulmonary resistance (TPR), pulmonary artery pressure (PAP) and arterial oxygen tension (PaO_2) during baseline, oxygen breathing and after isosorbide ingestion (mean ± standard deviation).

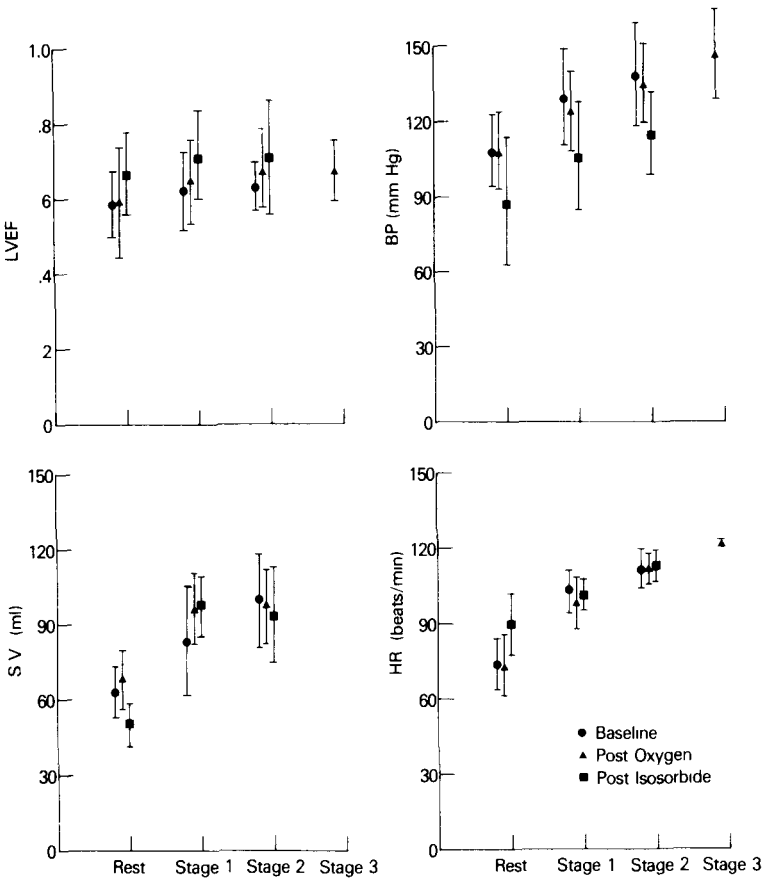


Figure 6. Rest and exercise left ventricular ejection fraction (LVEF), blood pressure (BP), stroke volume (SV) and heart rate (HR) during baseline, oxygen breathing and after isosorbide ingestion (mean ± standard deviation).

disease have noted a significant inverse relation between rest pulmonary artery pressure and right ventricular ejection fraction. This type of relation has also been noted in a group of patients with cardiac conditions that excluded intracardiac shunts (19). Other studies were unable to demonstrate a significant relation between the pulmonary artery pressure and right ventricular ejection fraction at rest in patients with chronic obstructive pulmonary disease (26), coronary artery disease (27) or aortic or mitral valve disease (28). A rest and exercise study of normal volunteers from our laboratories demonstrated a significant relation between total pulmonary resistance and right ventricular ejection fraction, but no significant relation was found between pulmonary artery pressure and right ventricular ejection fraction (17).

The reasons for discrepancies between studies like these are germane to the attempt, in this study, to relate rest and exercise right ventricular function to simultaneously measured hemodynamic variables. Our view is that right ventricular systolic function is afterload dependent and pulmonary artery pressure and total pulmonary resistance are components or indexes of afterload *but* neither of these measures is the sole determinant of right ventricular afterload *and* afterload is not the sole determinant of right ventricular systolic function (20). In an analysis of right ventricular function in a heterogeneous group of cardiopulmonary conditions, we noted the roles of: 1) tricuspid regurgitation as an afterload factor, 2) right ventricular ischemia or infarction as inferred from right coronary artery lesions and inferior left ventricular wall motion abnormalities, and 3) marked reduction of left ventricular systolic function (20).

Role of coronary artery disease. The initial objectives of this study of patients with chronic obstructive pulmonary disease included looking at the effects of multiple interventions on cardiac performance in *pure* pulmonary disease. For that reason, a rigorous attempt was made to exclude patients with any clinical suggestion of primary cardiac disease. Despite the absence of clinical or rest and exercise electrocardiographic evidence of coronary artery disease, one patient had a rest and exercise wall motion abnormality strongly suggesting coronary disease. Patients with this degree of lung disease will stop exercising because of dyspnea long before maximal heart rates are achieved (29). For this reason, neither exercise thallium nor exercise ventriculography is nearly as sensitive or specific in screening for coronary artery disease in patients with chronic lung disease as in other patient groups. The implication is that coronary artery disease cannot be reasonably excluded in patients with lung disease without coronary angiography. As suggested previously, coronary disease, especially right coronary disease with concomitant right ventricular infarction or mul-

JACC Vol 2, No. 4
October 1983 652–60

tiple vessel disease with rest or exercise reduction in global left ventricular function, could be expected to significantly alter the relations between ejection fractions and hemodynamics (20).

Role of right heart failure. An additional consequence of attempting to exclude primary cardiac disease occurred as a result of excluding patients with a history of biventricular congestive heart failure who were receiving digitalis, diuretic drugs or medication for afterload reduction. Because of the difficulty in clinically separating right heart failure secondary to chronic obstructive pulmonary disease from right heart failure secondary to left heart failure (23,24), it is likely that some patients with only cor pulmonale were excluded. The result is that only one of the nine subjects had a pulmonary artery mean pressure at rest greater than 20 mm Hg. Accordingly, this study examines a narrow range of rest pulmonary artery pressures. It is true that most patients with chronic obstructive pulmonary disease have only mild elevations of pulmonary artery pressure at rest, which is the reason that exercise is frequently necessary to see hemodynamic changes with oxygen (8). On the other hand, it is likely that the inclusion of patients with clinical right heart failure would have produced a far wider range of hemodynamic data.

Effect of medications. Another important complicating influence is the effect of medications. Both aminophylline and beta-agonist medications have been reported to increase ejection fractions in some patients with chronic lung disease (30,31). When this study was begun, consideration was given to withholding patients' medications. An example of the problems that can occur with this approach is summarized: One patient, with an $FEV_1 = 0.7$ liter/min was asked to discontinue aminophylline for 24 hours; he reported to the catheterization laboratory dyspneic at rest, audibly wheezing, with 25 mm Hg of pulsus paradoxus. After an intravenous loading dose of aminophylline, he improved symptomatically and had 6 mm Hg of pulsus paradoxus. He was subsequently able to perform the test. Recognizing the effects of these medications emphasizes the importance of comparing each patient with himself. It also provides an additional source of error in pooled data. Thus, the attempt to discontinue medications for study purposes is medically dangerous and at the same time changes the patient from the setting to which one would ultimately like to apply the study results.

Potential errors in measurement. All of the primary measurements used in this study (vascular pressures, cardiac output, right ventricular ejection fraction and left ventricular ejection fraction) are subject to large potential errors, especially at exercise in patients with chronic obstructive pulmonary disease (32–34). With exercise, all of these subjects developed greater than 10 mm pulsus paradoxus in their blood pressure recordings and all had greater than 10 mm Hg respiratory variations in central venous pressure, pulmonary artery systolic pressure and pulmonary wedge pressure. Because intrapleural pressure is not necessarily uniform and because intraesophageal pressure does not necessarily reflect intrapleural pressure, especially in a supine subject, there is no well established way to "correct" these pressures or average their variations (32,33). For this study, the electrical mean pressure averaged over three respiratory cycles was used. This type of problem must be taken into account when attempting to determine the significance of relations between "measured" pressures and other variables, such as resistance, calculated from these pressures.

The large intrathoracic pressure variations raise the possibility that flow may also be uneven. If this were the case, flow measured over a period that is short relative to respiration might be different from flow measurements averaged over time. Additional potential sources of problems with the thermodilution method include the development of subclinical pulmonary regurgitation or tricuspid regurgitation or opening of a foramen ovale—all of which can occur with patients with pulmonary hypertension expecially at exercise. The correlation of left and right ventricular stroke counts suggests that significant regurgitation or shunting did not occur in these subjects.

Methodologic factors. Considerable controversy has attended the efforts to derive right ventricular ejection fraction measurements from gated blood pool radionuclide ventriculography (34). The method used in this study has been validated in rest studies that included patients with abnormal right heart hemodynamics and function (16). As stated in the methods paper (16), although the computer edge detection programs are used to initially select regions of interest, it is frequently necessary for the operator to alter these regions, especially the frames from ventricular systole. As the degree of right heart abnormality increases, particularly with right heart dilation, the intervention becomes more frequent and more difficult. This problem does not occur with analysis of the left ventricle. Thus, the correspondence of left and right ventricular stroke counts strongly supports the validity of the measurements made in this study. Clearly, the presence of significant tricuspid or pulmonary regurgitation would make it impossible to use these "standards." These data continue to support the feasibility of such measures in patients with severe abnormality at exercise as well as at rest.

In light of the significant complicating features cited, it is not surprising that disparate results have been obtained when the right ventricular ejection fraction has been compared with hemodynamic measures in patients with chronic lung disease (18,26). An awareness of these factors provides insight into the seemingly contradictory results that can accrue from pooling the results from many patients. For example, in this study, low flow oxygen appears to decrease pulmonary resistance at stage I exercise but to have no effect at stage II. This is clearly because it is the sickest patients

who have the greatest response to oxygen and who could only complete one stage of exercise. In addition, sicker patients, that is, patients with worse obstruction of airways, also had greater intrathoracic pressure variations, thereby compounding the difficulties of measuring pressure and flow.

It is possible that some of the changes that appear only as trends in this study might reach statistical significance were there more patients; examples include exercise ejection fractions before and after oxygen. At the same time, inclusion of patients with right heart failure, patients with left heart disease and those taking different medications could alter the data in a variety of ways.

Clinical implications. It might be concluded from a study such as this that the attempt to exclude the effects of concomitant heart diseases and drugs and accurately measure and relate the rest and exercise ejection fractions and hemodynamic variables in patients with chronic obstructive pulmonary disease is a practical impossibility. It is our conclusion that such an attempt is necessary if we are to answer such basic questions as, What is the role of oxygen therapy in chronic obstructive pulmonary disease? Or, What is the effect of vasodilators on hemodynamics in chronic obstructive pulmonary disease? In addition, attempts to "simplify" the endeavor by turning to animal models have frequently so distorted the problem as to obfuscate rather than clarify. This study is a preliminary attempt to answer these questions and an even more preliminary endeavor to establish a basic methodology for evaluating mechanisms of heart and lung dyspnea. With regard to the former it says simply: low flow oxygen can lead to improved right and left ventricular ejection fractions in some patients with chronic obstructive pulmonary disease. It appears to do this most frequently during exercise and seems related to decreases in pulmonary pressure or resistance, but might also favorably affect left and right ventricular ischemia, thereby improving contractile function. Isosorbide dinitrate can lower filling and afterload pressures at rest and during exercise in patients with lung disease and may improve ejection fraction. These improvements may be accompanied by significant decreases in cardiac output and arterial oxygen tension at rest in a given patient.

We thank Benjamin Burrows, MD, Michael Lebowitz, MD, and John Seidenfeld, MD, of the Pulmonary Division, University of Arizona, Gordon Ewy, MD, Cardiology Section, University of Arizona and Murry Katz, MD, Associate Chief of Staff for Research, Tucson VA Medical Center, for their thoughtful reviews and helpful suggestions. Advice in statistical analysis was provided by A. Larry Wright, PhD, Mathematics Department, University of Arizona

We also thank the following for their technical assistance: Janis Marshall, Ann Colemen, Kaye Gaines, Cynthia Thomas, Carol Alcock, Lorelle Lambert, Charles Hougland, Bruce Mason, Ray Morris, Claudia French, Roger French and Billie McDermott, also Sharon Boykin for her clerical assistance and Gwen Roeske for her illustrative work

References

1. Fishman AP. Hypoxia on the pulmonary circulation How and where it acts. Circ Res 1976;38:221–31
2. Block AJ, Boysen PG, Wynne JW The origins of cor pulmonale. a hypothesis (editorial). Chest 1979;75.109.
3. Boysen PG, Block AJ, Wynne JW, Hunt LA, Flick MR. Nocturnal pulmonary hypertension in patients with chronic obstructive pulmonary disease. Chest 1979;76:536–42.
4. Abraham AS, Cole RV, Bishop JM Reversal of pulmonary hypertension by prolonged oxygen administration to patients with chronic bronchitis Circ Res 1968;23:147–57
5. Stark RD, Finnegan P, Bishop JM. Daily requirement of oxygen to reverse pulmonary hypertension in patients with chronic bronchitis. Br Med J 1972;3·724–8
6. Stark RD, Finnegan P, Bishop JM Long-term domiciliary oxygen in chronic bronchitis with pulmonary hypertension Br Med J 1973;3:467–70
7. Neff TA, Petty TL. Long-term continuous oxygen therapy in chronic airway obstruction; mortality in relationship to cor pulmonale hypoxia, and hypercapnia. Ann Intern Med 1970;72:621–6.
8. Burrows B Arterial oxygenation and pulmonary hemodynamics in patients with chronic airways obstruction Am Rev Resp Dis 1974;110:64–70.
9. Neff TA. Selection of patients for oxygen therapy (editorial) Chest 1975;68:481–2
10. Oxygen Therapy Committee of the ATS Scientific Assembly on Clinical Problems Oxygen administration in the home. Am Rev Resp Dis 1977;115:897–9.
11. The Nott Study Group. Is 12-hour oxygen as effective as 24-hour oxygen in advanced chronic obstructive pulmonary disease with hypoxemia? (the Nocturnal Oxygen Therapy Trial—NOTT). Chest 1980;78.419–26.
12. Danahy DT, Tobis JM, Aronow WS, Chetly K, Glauser F. Effects of isosorbide dinitrate on pulmonary hypertension in chronic obstructive pulmonary disease. Clin Pharmacol Ther 1979,25.541–8.
13. Kontetzko N, Schlehe H, Harich B, Matthys H. Effect of isosorbide dinitrate on hemodynamics and respiration of patients with coronary artery disease and of patients with chronic cor pulmonale. Respiration 1975,32·368–77
14. Hales CA, Westphal D. Hypoxemia following the administration of sublingual nitroglycerin Am J Med 1978;65:911–8.
15. Simonneau G, Escourrou P, Duroux P, Lockhart A. Inhibition of hypoxic pulmonary vasoconstriction by nifedipine. N Engl J Med 1981;304:1582–5
16. Morrison DA, Marshall J, Wright AL, Daly M, Henry R. An improved method of right ventricular gated equilibrium blood pool radionuclide ventriculography Chest 1982;82:607–14.
17. Morrison DA, Sorenson SC, Caldwell JH, Ritchie JL, Kennedy JW. The normal right ventricular response to supine exercise. Chest 1982,82.686–91
18. Brent B, Berger H, Matthay RA, Mahler R, Pytlik L, Zaret BL. Pathophysiologic correlates of right ventricular ejection in chronic obstructive pulmonary disease: a combined radionuclide-hemodynamic study. Am J Cardiol 1982;50:255–62
19. Korr KS, Gandsman EJ, Winkler ML, Shulman RS, Bough EW. Hemodynamic correlates of right ventricular ejection fraction measured with gated radionuclide angiography. Am J Cardiol 1982;49:71–2
20. Morrison DA, Goldman S, Henry R, et al The effect of pulmonary hypertension on systolic function in the right ventricle. Chest (in press)
21. Goldman HI, Becklake MR. Respiratory function tests: normal values of median altitudes and the prediction of normal results. Am Rev Tuberc 1959;79:457–67.

22 Norris J, Kaski A, Johnson J. Spirometric standards for healthy nonsmoking adults. Am Rev Resp Dis 1971;103:57–67.

23. Unger K, Shaw D, Karliner JS, Crawford M, O'Rourke RA, Moser KM. Evaluation of left ventricular performance in acutely ill patients with chronic obstructive lung disease. Chest 1975;68:135–42.

24 Bahler RC. Assessment of left ventricular function in chronic obstructive pulmonary disease (editorial). Chest 1975;68:132–3

25. Smith TD, Richards P. A simple kit for the preparation of ^{99m}TC-labeled red blood cells. J Nucl Med 1976;17:126–31.

26 Ellis JH, Kirch D, Steele PP. Right ventricular ejection fraction in severe chronic airway obstruction. Chest 1977;71(suppl):281–2.

27. Wells DE, Befeler B. Dysfunction of the right ventricle in coronary artery disease. Chest 1974;66:230–5.

28. Winzelberg GG, Boucher CA, Pohost GM, et al. Right ventricular function in aortic and mitral valve disease. Chest 1981;79:520–8

29. Wasserman K, Whipp BJ. Exercise physiology in health and disease In: Murray JF, ed. Lung Disease–State of the Art 1974–75 New York: American Lung Association, 1975.321–51

30. Matthay RA, Berger HJ, Loke J, Gottschalk A, Zaret BL. Effects of aminophylline upon right and left ventricular performance in chronic obstructive pulmonary disease Am J Med 1978;65:903–10

31. Brent BN, Mahler D, Berger HJ, Matthay RA, Pytlik L, Zaret BL. Augmentation of right ventricular performance in chronic obstructive pulmonary disease by terbutaline: a combined radionuclide and hemodynamic study. Am J Cardiol 1982;50:313–9.

32. Rice DL, Awe RJ, Gaasch WH, Alexander JK, Jenkins DE Wedge pressure measurements in obstructive pulmonary disease Chest 1974;66:628–32.

33. Bahler RC, Chester EH, Behman MJ, Baum GL. Multidisciplinary treatment of chronic pulmonary insufficiency. 4. The influence of intrathoracic pressure variations on increases in pulmonary vascular pressure during exercise in patients with chronic obstructive pulmonary disease. Chest 1977,72:703–8.

34. Berger HJ, Matthay RA. Radionuclide right ventricular ejection fraction. applications in valvular heart disease (editorial). Chest 1981;79:497–8